REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 33-69 will be pending in the application subsequent to entry of this Amendment of which claims 55-64 have been withdrawn.

Claim 33 has been amended for purposes of clarity as explained in the remarks that follow.

The Examiner has raised objection that the energy acceptor of Claim 33 is missing the structural element of a moiety with a negative charge to allow the energy acceptor (stated by the Examiner to be positively charged) to be electrically neutral.

Applicant points out that the energy acceptor is not necessarily positively charged. Various of the optional substituents in the energy acceptor (SO_3^-, PO_3^{2-}, COO^-) are negatively charged. Therefore, the energy acceptor as a whole may be positively charged, neutral or negatively charged. Where the energy acceptor is charged, the reagent may comprise an appropriate counterion (as in Claim 50, which includes both negative and positive counterions). In order to reduce issues and advance examination claim 33 has been amended to state that the reagent optionally comprises a counterion.

Claim 42

The Examiner has raised objection that the concept of a linkage lacks antecedent basis in Claim 33. The basis for this objection is not understood. Claim 42 specifies that "the energy donor and the energy acceptor are not linked in the absence of analyte", and does not refer to a linkage.

Claims 45 and 50

These objections have been addressed by the above claim amendments. The comments on Claim 33 are also relevant to the objection to Claim 50.

35 USC 103 Objections

The Examiner has raised objection that Claim 33 is not inventive over a combination of Cote et al. (US 6,485,703), Lu et al. (US 2002/0102267) as evidence document, Thurmond et al. (US 2004/0259206), Owen et al., STN Registry file print out for Crystal Violet and Matzuk (WO 89/09833). The basic combination of references is carried on for all five rejections of the various claims. The following comments are directed to and are in defense of claim 33 from which all of the examined claims depend.

The Examiner takes the view that it would be obvious to modify the FRET assay of Cote et al. by replacing the TRITC quencher with Doebner's Violet (disclosed in Matzuk), since Thurmond et al. discloses that triphenylmethanes are suitable quenchers in a FRET assay, Owen teaches that crystal violet (a triphenylmethane) can quench fluorescein and Doebner's Violet is also a triphenylmethane.

This objection suffers from various major difficulties and is traversed.

None of prior art discloses the claimed energy acceptor structure

First, and most significantly, the Examiner's assertion that "the structure of Doebner's Violet meets the limitations of the structure of Claim 33 since Doebner's Violet comprises a triphenylmethane rings structure wherein R^1 to R^3 are electron donating substituents… and the remaining R groups are hydrogen" is incorrect. Doebner's Violet is not an energy acceptor as defined in current Claim 33. Claim 33 requires that "at least one of R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} [the *ortho* groups] is O-alkyl", and in Doebner's Violet each *ortho* group is hydrogen.

Therefore, the combination of prior art cited by the Examiner does not lead to a reagent as claimed in Claim 33. No energy acceptor as defined in Claim 33 has been identified anywhere in the prior art, and no suggestion has been made that it would be obvious to modify Doebner's Violet or any other prior art structure to reach the energy acceptor of Claim 33. As a result, there is no "obviousness".

Skilled person would not combine large number of teachings from different technical fields

Second, this objection relies on a combination of 5 documents[1] (excluding the evidence document). It would not be obvious to the skilled person to combine this number of separate

[1]. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961); *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 U.S.P.Q. 121, 124 (7th Cir. 1950); *Reynolds et al v. Whitin Machine Works*, 167 F.2d 78, 83, 76 U.S.P.Q. 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 U.S.P.Q. 902, 927 (N.D. Ala. 1980). Indeed, the inference that can be taken from the large reference citation is that not one reference is on point and that the patentee has clearly accomplished what the prior art has repeatedly failed to do. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961).

teachings without any motivation to do so (e.g. the benefit of hindsight available to the Examiner). This is particularly the case as the documents are patent documents and scientific papers, which would not form part of the skilled person's general knowledge. Owen et al. is an old teaching dating from 1972, and the skilled person would be unlikely to combine it with more recent documents without motivation to do so.

The problem of combining the teachings is compounded by the fact that the teachings lie in very different technical fields. Cote et al. relates to a glucose sensor. Thurmond et al. relates to a monkey protein. Owen et al. relates to dye intermolecular interactions. The STN print out relates to a particular chemical compound. Matzuk relates to pharmaceutical agents. It is not plausible that the relevant skilled person would be aware of all these teachings, let alone that he would seek to combine them.

No motivation in prior art to modify FRET assay of Cote et al. to use Doebner's Violet

Third, the prior art provides no motivation to use Doebner's Violet instead of TRITC in the FRET assay of Cote et al.

Cote et al. itself does not identify any problem with the use of TRITC. It suggests (col. 21, lines 29-30) a variety of reporter compounds which can be used, but does not suggest the use of triarylmethane dyes. Thurmond et al. mentions the broad class "triphenylmethanes" briefly at the end of a long list of possible quencher moieties for use in FRET, and does not suggest such quenchers as an alternative to TRITC. No further information or examples in relation to triphenylmethanes are given, and no advantages are suggested. Owen et al. and Matzuk contains no reference to FRET. Matzuk includes Doebner's Violet as one entry in a list of dye compounds covering many pages.

The Examiner has stated that "The ordinary artisan would have been motivated [to] substitute Doebner's Violet for TRITC because each energy acceptor is known to have the same function, accepting energy from a fluorescent energy donor… The ordinary artisan would have had a reasonable expectation than one could substitute Doebner's Violet for TRITC as the energy acceptor since CV, which has the same triaryl structure as Doebner's Violet, is known to quench the fluorescence of fluorescein."

With respect, this analysis is too simplistic.

The skilled person having read Cote et al., which refers to "any dye pair that results in FRET" (col. 21, lines 30-31) would appreciate that FRET requires an energy donor-energy acceptor pair which interact effectively. He would understand that changing the energy acceptor of the effective FRET pair of Cote et al. (FITC and TRITC) to a different energy acceptor might well lead to a loss of FRET, and would proceed cautiously.

Owen et al. deals with the basic science of dye intermolecular interactions rather than to applications such as FRET. Nothing in Owen et al. indicates that the quenching of fluorescein by Crystal Violet would be adequate to allow these molecules to act as a FRET pair. Indeed, applicant's understanding of Fig. 1 of Owen et al. is that of the four dyes shown (Erythrosin, Rose Bengal, Eosin and fluorescein), fluorescein is the least effectively quenched by Crystal Violet (as the fluorescein curve has the lowest gradient).

Moreover, of course, the differences in structure between Doebner's Violet and Crystal Violet would lead to different energy acceptor characteristics, and there is no information on how Doebner's Violet would behave as an energy acceptor.

Thus, nothing in the prior art would motivate the skilled person to us FITC and Doebner's Violet as a FRET pair.

Moreover, the FRET pair of Cote et al. is intended for *in vivo* use (Claim 1 of Cote et al.). Nothing in the prior art suggests that Doebner's Violet would be appropriate in this context.

Claimed invention has advantages

Finally, applicants point out that the energy acceptors of Claim 33 have various advantages as set out on page 31 of the application:

- they are resistant to degradation as a result of the ortho groups which are not present in Doebner's Violet

- they can be used with a variety of donors

- they are suitable for *in vivo* use

- their performance is predictable

- they do not contribute to background fluorescence signal

These advantages are not identified in the prior art, but were found by the present inventors.

For these reasons it is respectfully submitted that all of the pending claims define patentable subject matter. Reconsideration and allowance are solicited. Should the examiner require further information, please contact the undersigned.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1140.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Arthur R. Crawford/
Arthur R. Crawford
Reg. No. 25,327

ARC:caw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100